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doi: 10.1111/joim.12167

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Health economic evaluation of treatments for Alzheimer's disease: impact of new diagnostic criteria

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Abstract. Wimo A, Ballard C, Brayne C, Gauthier S, Handels R, Jones RW, Jonsson L, Khachaturian AS, Kramberger M (Karolinska Institutet, Stockholm, Uppsala University/County of Gävleborg, Gävle, Sweden, King´s College London, London, Cambridge University, Cambridge, UK, Douglas Mental Health Research Institute, Montreal, QC, Canada, Maastricht University, Maastricht, The Netherlands, The Research Institute for the Care of Older People (RICE), Bath, UK, Campaign to Prevent Alzheimer's Disease by 2020 and University Medical Centre Ljubljana, Ljubljana, Slovenia). Health economic evaluation of treatments for Alzheimer's disease: impact of new diagnostic criteria. (Key Symposium). *J Intern Med* 2014; **275**: 304–316.

The socio-economic impact of Alzheimer's disease (AD) and other dementias is enormous, and the potential economic challenges ahead are clear given the projected future numbers of individuals with these conditions. Because of the high prevalence and cost of dementia, it is very important to assess any intervention from a cost-effectiveness viewpoint. The diagnostic criteria for preclinical AD suggested by the National Institute on Aging and Alzheimer's Association workgroups in combination with the goal of effective disease-modifying treatment (DMT) are, however, a challenge for clinical practice and for the design of clinical trials. Key issues for future cost-effectiveness studies include the following: (i) the consequences for patients if diagnosis is shifted from AD-dementia to predementia states, (ii) bridging the gap between clinical trial populations and patients treated in clinical practice, (iii) translation of clinical trial end-points into measures that are meaningful to patients and policymakers/payers and (iv) how to measure long-term effects. To improve cost-effectiveness studies, long-term population-based data on disease progression, costs and outcomes in clinical practice are needed not only in dementia but also in predementia states. Reliable surrogate end-points in clinical trials that are sensitive to detect effects even in predementia states are also essential as well as robust and validated modelling methods from predementia states that also take into account comorbidities and age. Finally, the ethical consequences of early diagnosis should be considered.

Keywords: Alzheimer's disease, clinical trials, dementia, diagnosis, health economics.

Introduction

Today, about 36 million people worldwide suffer from Alzheimer's disease (AD) and other dementias [1]. This figure is projected to more than double by 2030 (65 million) and reach about 115 million in 2050 unless there are major improvements in prevention and/or cure. This increase will be greatest in low- and middle-income countries (LMICs) where it will be roughly exponential, whilst in high-income countries (HICs), the increase will be more linear.

Symptomatic treatment of AD with acetylcholine esterase inhibitors and memantine has been available since the 1990s, but no cure or disease-modifying treatment (DMT) for AD is available today, despite extensive research in this area. Epidemiological research has suggested several risk and protective factors for dementia, giving hope for prevention approaches that modulate the risk of dementia including lifestyle factors such as more physical exercise and weight reduction and medical factors such as hypertension, elevated cholesterol and diabetes. These provide potential

opportunities to reduce the risk of dementia at least partially [2], and there is some evidence to indicate that this is already happening based upon reduced age-related incidence and prevalence rates [3, 4].

The socio-economic impact of dementia disorders is enormous. In 2010, the worldwide societal costs were estimated at US$ 604 billion, which constitutes approximately 1% of the aggregated global gross domestic product [5, 6] (Fig. 1) with the greatest proportion of costs from HICs. There is a huge impact of informal care throughout the world, particularly in LMICs where resources in the social care sector are scarce. The potential economic challenges ahead are clear given the projected future numbers of individuals with dementia. However, the challenges vary in different parts of the world; in HICs, the challenge seems to be funding of long-term care, whereas in LMICs, establishing a social care sector is most important. The greatest challenge for all is to develop effective management, treatment and cure (where possible). Given the high prevalence and cost of dementia, it is important to assess any such intervention from a cost-effectiveness viewpoint.

Any type of intervention/treatment includes a diagnostic process. One of the key controversies has been the magnitude of benefit conferred to individuals through early diagnosis and access to clinical and care services in the absence of DMTs. Whilst some view the benefits as limited, others argue for offering early diagnosis of AD, highlighting the value of information, family support, care planning and signposting and the importance for individuals of being able to take control of decisions regarding their own treatment and care whilst they retain capacity (given the assumption that the diagnosis is correct) [7]. The true value of these interventions and other aspects of service support are difficult to determine from the currently available evidence. A substantial and cost-effective positive impact on quality of life was demonstrated in an open study of memory clinic services, but this finding was difficult to interpret in the absence of a control group [8]. By contrast, randomized controlled trials (RCTs) focusing on specific aspects of service delivery such as information, education, signposting and case management have delivered benefits with only a small standardized effect size [9], indicating difficulty in testing whether the interventions are cost-effective. Although difficult to conduct, cluster RCTs (preferably several in various settings and populations) to examine the benefits associated with early diagnosis supported by a comprehensive service model are essential to inform planning and service development.

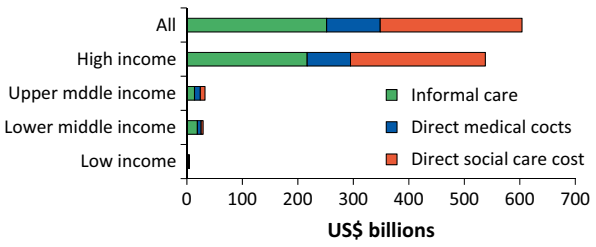

Fig. 1 *Estimated global aggregated costs of dementia care in 2010 in different income groups according to the World Bank [6].*

A great challenge in differential diagnosis of dementia or predementia subtypes [i.e. preclinical, mild cognitive impairment (MCI) or early dementia] is that there is no single test or diagnostic tool that confirms the diagnosis. An AD diagnosis is, for example, based on a comprehensive but varying mixture of clinical examinations, laboratory, genetic and neuropsychological tests and analyses of biomarkers [e.g. cerebrospinal fluid (CSF) markers and different imaging methods].

The previously [10] and recently by the National Institute on Aging and Alzheimer's Association workgroups [11–13] suggested new diagnostic criteria for preclinical AD, AD-MCI and AD-dementia include both recommendations for clinical practice without access to advanced diagnostic tools and recommendations for research. Although the research criteria include the use of biomarkers, it was nevertheless concluded by the workgroups [11–13] that much validation work is still needed.

Furthermore, much interest today in predementia diagnosis of AD (preclinical and/or MCI) is linked to the hope for effective DMT. If powerful DMTs become available, being able to recognize AD cases at a very early stage (i.e. in the preclinical phase) would represent enormous progress both for patients with subtypes of predementia and for their families. However, at present without the availability of DMTs, the arguments for diagnosis of preclinical AD or MCI-AD are for many reasons more complex and controversial. Here, we will discuss this issue from a health economic viewpoint. Although the focus will be on AD, it is

sometimes not possible or meaningful to separate AD from other dementias. Thus, we may consider the preclinical phase and MCI either separately or combined as predementia states. These terms are used to identify the implications of the new diagnostic criteria. However, from an epidemiological viewpoint, the concept 'at risk' rather than 'preclinical' might be more appropriate as the latter supposes that the prediction will be accurate even though (as noted herein) a substantial proportion of individuals could be expected never to develop the disorder.

Health economic issues

Cost of illness

Cost of illness (COI) studies, such as the estimate of global costs [14], are descriptive and cannot be used to specify allocations of resources for treatment. COI studies can describe how costs are distributed amongst payers and how costs change over time. In dementia care, it is already known that the most important cost drivers are long-term institutional care and the societal value of informal care. Another conclusion from COI studies is that we are primarily seeing the 'wrong' type of costs; costs of dementia mainly comprise resources lost due to disease or resources used to cope with the consequences of disease. Only a small fraction of resources are spent on activities to prevent or delay disease onset and progression.

Cost-effectiveness

Cost-effectiveness analysis is a tool that is used to assess efficiency in resource allocation and to guide decisions on the introduction and use of new technology [15]. It has a formal place in the process for assessing new pharmaceutical products in a number of countries and is used informally across most markets.

Reports of empirical cost-effectiveness studies are rare. In a systematic review of dementia by the Swedish health technology assessment institute SBU [16], only five such studies were identified in which drugs for AD were analysed. For nonpharmacological interventions, the situation was the same – only a few studies were identified. On the other hand, more economic evaluations based on simulations have been reported.

Implications of the new diagnostic criteria

From a health economic viewpoint, any diagnostic process raises questions: can cost-effectiveness of diagnostics *per se* be discussed (has a diagnosis alone any value?) or must there be a link between the diagnosis and some type of treatment/intervention/other outcome?

In AD diagnosis, there are several potential pathways before a diagnosis is established and the list of diagnostic tools in Table 1 reflects the options that are recommended by, for example, the European Federation of Neurological Societies [17]. Different tools are available and their accuracy, costs, optimum number and sequence of use can be considered. If diagnosis of AD is to move from AD-dementia to predementia AD states (such as AD-MCI), the first two diagnostic options shown in Table 2 [primary care (PC) alone and PC plus specialist clinical examination only (SCE)] are unlikely to be appropriate. When a set of tools is introduced into the diagnostic process, there is considerable variation in the costs (as seen in Table 2), according to which and how many tools are used.

Additionally the validity and reproducibility of tools are important. Any diagnostic tool [clinical examination, neuropsychological testing, magnetic resonance imaging (MRI) or CSF biomarkers] with a potential important additive value for the diagnosis of AD should therefore be used in a standardized way. Harmonization of protocols decreases the need for replication and can reduce the diagnostic costs in routine clinical practice.

Table 1 *The ability of different diagnostic tools to detect different levels of cognitive impairment*

	Clinical examination	Neuropsychology	PET	MRI	CSF
AD-dementia	xx	xxx	xx	xx	xx
AD-MCI	x	xx	xx	xx	xx
Preclinical AD	0	x	x	x	xx

AD, Alzheimer's disease; MCI, mild cognitive impairment; PET, positron emission tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid biomarkers; 0, not possible; x, fair; xx, good; xxx, very good.

Table 2 *Examples of different diagnostic pathways when AD is suspected*

Diagnostic pathway	Sequence of tests	Cost (US$)*
Dia1	PC	860
Dia2	PC+SCE	1330
Dia3	PC+SCE+MRI	1700
Dia4	PC+SCE+CSF	2130
Dia5	PC+SCE+NP	1870
Dia6	PC+SCE+PET	2760
Dia7	PC+SCE+MRI+CSF	2500
Dia8	PC+SCE+MRI+NP	2240
Dia9	PC+SCE+MRI+PET	3130
Dia10	PC+SCE+CSF+NP	2670
Dia11	PC+SCE+CSF+PET	3560
Dia12	PC+SCE+NP+PET	3300
Dia13	PC+SCE+MRI+CSF+NP	3040
Dia14	PC+SCE+MRI+CSF+PET	3930
Dia15	PC+SCE+MRI+NP+PET	3670
Dia16	PC+SCE+CSF+NP+PET	4100
Dia17	PC+SCE+MRI+CSF+NP+PET	4470

Dia, diagnostic pathway, PC, primary care (includes clinical examination, laboratory tests, computed tomography scan and the Mini-Mental State Examination); SCE, specialist clinical examination (only); MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; NP, neuropsychological examination; PET, positron emission tomography.
*US$ 1 ≈ 7 SEK.

However, harmonization is not usually achieved as addressed by the European Alzheimer's Disease Consortium [18] and the European Alzheimer's Disease Neuroimaging Initiative [19]. It remains unclear whether it is possible to identify an optimal diagnostic pathway, which is generalizable across populations. The marginal cost for each additional new case that is identified when a new tool is added to the diagnostic process may be high, but such an analysis has yet to be reported. Such studies are urgently needed and require a gold standard method with an evaluation of the benefits not only of finding new cases but also of avoiding false-positive (FP) and false-negative (FN) cases when more tools are included in the process.

The diagnostic process when AD is suspected also takes time, from the first awareness of the possibility and symptoms to initial contact with health care (often PC) and to the day of diagnosis. If this diagnostic uncertainty shifts from dementia to predementia states, the time window from early diagnostic procedures to a definite diagnosis (or a statement – at least temporarily – that AD is not suspected) may be several years during which time the person must live with this uncertainty and will be very likely to require repeat clinic visits and undergo further investigations. This period of uncertainty and medicalization may lead to additional stress and loss of quality of life during possibly the last period of an older person's life. In individuals at an earlier stage of life, this uncertainty and medicalization may also lead to losses in terms of sick leave and production. Being labelled as 'being at increased risk of AD' may have potential negative implications for individuals; the impact of this is unknown at present as current evidence is based on informing individuals who have volunteered for research as a result of their family history. To inform this debate, we will need to know from the population how individuals will respond to knowledge of risk over prolonged periods and be able to provide them with evidence of how accurate that risk prediction might be (i.e. in how many individuals the prediction of increased risk will be incorrect). How this period of uncertainty should be valued in economic terms is unclear. And if science storms ahead but is not in tandem with society, this might have economic consequences not only for individuals but also for society.

Besides the psychological consequences of an early diagnosis, the diagnostic methods themselves may have (potential) side effects. For example, if a large number of individuals undergo lumbar puncture (for CSF sampling), computed tomography (CT), positron emission tomography (PET) (including the newly available amyloid imaging techniques) or MRI investigations as a consequence of the introduction of DMT with a need for comprehensive diagnostics, there may be a significant number of side effects (perhaps particularly with CSF sampling) with economic consequences that need to be considered.

The age of the target population also needs to be taken into account. Even if a 'pure AD'-type pathology contributes to the cognitive decline in the 'oldest old' (i.e. ≥85 years old), based on our knowledge of the underlying pathology, it is likely that comorbid conditions are involved [20]. Figures for the sensitivity and specificity of new investigations as

well as the positive (PPVs) and negative predictive values (NPVs) are derived from selected populations from specialized memory clinics that are mostly younger than those with the 'usual' dementias seen in the oldest old [21]. Thus, the potential benefits of diagnosis and the magnitude of treatment benefits need to be considered and weighed against the side effects and burden. From a cost-effectiveness viewpoint, this means that the costs of diagnosis and treatment may not be offset sufficiently as the benefits in terms of outcome may be limited. For the oldest patients, other care strategies may be more cost-effective. However, this is not an argument for fixed age restrictions in general as individuals' situation and health status should always the most important criteria as well as their likelihood of benefit from treatment, given their age and comorbidities.

One important question therefore is whether we should aim to diagnose preclinical AD, AD-MCI or AD-dementia. In terms of consequences, we must include not only all true-positive (TP) and true-negative (TN) cases (based on a gold standard and in relation to diagnostic criteria), but also FP and FN cases. What are the trade-offs in terms of cost-effectiveness if the diagnosis is linked to treatment (i.e. benefits for TPs but disadvantages for non-treated FNs and both disadvantages and side effects for treated FPs)? Even if it is possible to calculate the costs for the different diagnostic pathways and the cost for each diagnosed TP case (and estimate the cost-effectiveness of treatment versus no treatment/usual care) and TN case, how should the consequences for FPs and FNs be valued. When most diagnoses of AD in clinical practice were for mild-to-moderate disease, the magnitude of this problem was not so great; however, if the diagnostic target group is moved from AD-dementia to AD-MCI (or even further to preclinical AD), particularly if a screening policy or systematic case finding is recommended, the situation will become very challenging, as illustrated in Table 3. The major problem will be the risk of FP cases as indicated by the PPVs. As mentioned above, at the individual level, there is an uncertainty about the classification of a person's risk of developing AD-dementia. Follow-up confirms whether or not classifications in terms of TP, TN, FP and FN were correct. It is difficult to estimate the consequences of living with a FP diagnosis of AD for several years from a cost-effectiveness viewpoint (the denominator in the incremental cost-effectiveness ratio ICER).

Is this situation unique for AD? Perhaps not, but a shift in the diagnostic spectrum from AD-dementia to predementia states will probably make the risk of FPs greater, because the diagnostics of AD is not straightforward.

As most studies on sensitivity and specificity are undertaken in highly specialized clinics (mainly university clinics with a high 'prevalence' of AD in the target population and a high level of resources), we cannot predict what will happen if diagnosis on a large scale moves to PC, and specialist clinics become a scarce resource. If effective DMTs become available, there may be demands for very early diagnosis (including screening). Then, sensitivity and specificity figures between, for example, 80 and 90% will be problematic (Table 3). The nature of the testing methods is important. Different types of screening can be used, such as mass screening (e.g. all persons 65 or older every 5 years), opportunistic screening (e.g. any person who enters any healthcare centre will be offered cognitive testing) or risk screening (e.g. only genetic risk groups). The World Health Organization (WHO) has recommended criteria for screening [22] (see Box 1), and it seems obvious that currently any screening programme for AD generally is problematic and hardly recommendable today.

However, if effective DMTs for AD were available, one solution may be a two-step approach, as shown in Table 3, with the aim of increasing the probability of cases with the disorder in the target population [16]. The first step may reflect activities in PC and the second step at the specialist level. In the Swedish SveDem registry, the cost of diagnostic activities in PC (including a clinical examination, a basic laboratory battery of tests, the Mini-Mental State Examination or similar and in many cases CT scanning of the brain) was 6800 SEK (approximately US$ 1000 or €800), and in specialist care (with varying use of MRI, PET and CSF and neuropsychological testing), the average cost was 11 700 SEK [23]. As well as the lower risk of FPs, there may also be cost savings in using PC as the first-level filter for diagnosis, but the risk of course is of FNs in PC.

Implications of new diagnostic criteria for clinical trials

Following the introduction of the new diagnostic criteria, the design of clinical trials will be challenging. Sample size estimates need to be considered. For economic evaluations, this has two

Table 3 *Examples of how different levels of prevalence, sensitivity and specificity affect the PPV and NPV under various conditions*

	Sensitivity and specificity 80% (%)	Sensitivity and specificity 90% (%)	Sensitivity and specificity 95% (%)	Sensitivity and specificity 99% (%)
Incident AD (1.6% of target population)				
PPV	6.3	13.0	24.1	62.3
NPV	99.6	99.8	99.9	99.9
AD-MCI or prevalent AD (7.4% of target population)				
PPV	24.2	41.9	60.3	88.8
NPV	98.0	99.1	99.6	99.9
Two-step approach (prevalence 25% of target population)				
PPV	57.1	75.0	86.4	97.1
NPV	92.3	96.4	98.3	99.7
Memory clinic (assumed prevalence 50%)				
PPV	80.0	90.0	95.0	99.0
NPV	80.0	90.0	95.0	99.0

AD, Alzheimer's disease; MCI, mild cognitive impairment; PPV, positive predictive value; NPV, negative predictive value.

implications; first for the efficacy results *per se* (which are crucial for modelling) and secondly for the within-trial analysis of resource utilization and cost-effectiveness. An experience from the studies where within-trial results on resource utilization and costs have been evaluated [24–27] shows that they are underpowered for economic evaluations. If there is a shift in trials from populations with AD-dementia to those with predementia states, there will be a need for sample size estimates for both efficacy and cost-effectiveness evaluations, probably also with a need for larger study populations and longer duration of trials. We will need better background data on both costs and outcomes in predementia states. Similar to diagnosis where several tools are needed, there is an interest in analysing the cost-effectiveness of combined treatment approaches (such as drug treatment with social support programmes) [28].

Implications of new diagnostic criteria for clinical practice

The introduction of new diagnostic criteria into clinical practice in parallel with the development of DMTs may lead to two extreme scenarios: (i) successful implementation of predementia diagnosis of AD (preclinical and/or AD-MCI), but no availability of DMTs due to trial failures; or (ii) availability of an effective DMT, but very limited diagnostic infrastructure to identify individuals who are suitable for treatment (i.e. in any window of modifiability).

To a varying extent, most patients with AD-dementia are diagnosed late or not at all [29]. Even if either of the extreme scenarios is unlikely to occur, we are now facing a new challenge in the management and diagnosis of AD. Many trials have failed, but there are still several DMT approaches in the pipeline. There may be demands of and possibilities for predementia AD diagnostics (with all the problems mentioned above). If the goal of diagnostics is to diagnose dementia, and the type of dementia, PC can provide the first level in the diagnostic process (although this opportunity is often not used in an optimal way). If the aim is predementia diagnosis, the two-step approach seems appropriate where PC is the filter before advanced specialist diagnosis. To some extent, this is the way it is organized today, but if effective DMTs become available, the magnitude of the potential target population will be large and there will be a high demand for diagnosis and care. Some type of infrastructure for early diagnosis would need to be established with PC as a filter. As the situation is today (WHO criteria; risk of FPs), this does not imply the need for mass screening but how to manage the potential increased demand must be considered. If DMTs are developed, it is also important to identify the most cost-effective diagnostic pathway at the specialist level (the

Box 1
Classic World Health Organization screening criteria [65]

1 The condition sought should be an important health problem.

2 There should be an accepted treatment for patients with recognized disease.

3 Facilities for diagnosis and treatment should be available.

4 There should be a recognizable latent or early symptomatic stage.

5 There should be a suitable test or examination.

6 The test should be acceptable to the population.

7 The natural history of the condition, including development from latent to declared disease, should be adequately understood.

8 There should be an agreed policy on whom to treat as patients.

9 The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

10 Case finding should be a continuing process and not a 'once and for all' project.

optimum number and most effective sequence of tests) as illustrated in Table 2.

Another practical consequence of effective DMTs is the potentially large number of predementia AD cases (TPs and FPs) that are identified and need support, treatment and ongoing care. The DMTs that are currently being considered (such as vaccination) have security and monitoring demands that makes a referral back to PC unlikely. Thus, many challenges can be anticipated including memory clinic visit volumes and equitable access to therapies. There will be prioritizing problems for decision-makers when demands occur for allocation of resources to memory clinics (e.g. versus cancer clinics). Another consequence of scarce resources might be a re-allocation away from care of patients with severe dementia to those with an early diagnosis, given the assumption that DMT will be successful. In such a situation, we need to have good instruments for cost-effectiveness analyses as a support in decision-making.

Current understanding of risk based on observational studies supports prevention through primary prevention and optimal management of vascular risk and is supported by projections from modelling of the population impact of such measures [30, 31]. Prevention activities in PC and wider society should be emphasized beyond the usual prevention of cardiovascular ill health [32].

A special situation may occur, for example, in the case of rare familial AD where gene therapy may be possible [33]. Even if individual costs for the diagnostics and treatment of rare diseases may be high, the total societal costs will be low because of the small number of affected persons, and thus, high costs may be justified if effective diagnostics and treatment become available.

Implications of new diagnostic criteria for reimbursement

Patients with AD receive care and support from many different formal and informal sectors of society. In HICs and in early disease states support is mainly received from the healthcare system (PC and specialist care) but, the social care sector (e.g. home or day care and long-term care) becomes more important as the disease progresses. Informal care makes an important contribution throughout the disease course. Interventions may have an impact on resource use and costs in different sectors, but it is unlikely that the benefits of interventions will be distributed similarly (both in terms of magnitude and time) compared to the benefits. At one extreme, the costs occur in one sector, but the benefits in another. If for example a very effective DMT is introduced, the health care sector will bear the costs for diagnosis and treatment and its reimbursement but most of the benefits will be seen later in the course of AD in the social care sector. Such a scenario was shown in a recently published hypothetical model [34]. Even if the intervention is cost-effective from a societal viewpoint, the imbalance is a problem (and may be labelled

Table 4 *Advantages and disadvantages of different study designs from a health economic viewpoint*

Design	Advantages	Disadvantages
Classic RCT	High internal validity	Selected populations; rarely powered for economic evaluations; short trial duration
Pragmatic RCT	Study population reflects clinical reality	Rarely powered for economic evaluations; not necessarily blinded
Registry	Large samples; long follow-up	Not controlled; no predefined hypotheses; heterogenous study populations; lack of important data (informal care); varied quality of diagnoses
Cohort/case–control study	Long follow-up; good representativity; both AD and non-AD cases	Not controlled; varied quality of diagnoses; may be few cases in cohort studies
Simulation	High external validity; different scenarios testable in sensitivity analysis; long-term effects	Not empirical in long-term estimates; inputs of varying quality; assumptions crucial

AD, Alzheimer's disease; RCT, randomized controlled trial.

as imperfect or even as a perverse incentive). Because an effective DMT is likely to be much more costly than current treatment (making reimbursement crucial) and a large number of individuals from an equity viewpoint will demand care, it is a challenge to avoid or regulate emerging imbalance.

Key methodological issues

Bridging the gap between clinical trial populations and patients to be treated in clinical practice

Study populations in AD clinical trials are in general younger and healthier with fewer concurrent comorbidities than AD populations in epidemiological studies and in clinical practice [35]. The decline in cognition may be faster in younger AD patients but the decline in functional outcomes may be slower, compared with older patients.

There are different ways to handle this situation. To make a comprehensive judgement of the cost-effectiveness of interventions in AD, it is necessary to synthesize the information and the conclusions need to be based on several types of inputs. Therefore the aim cannot be to identify the single ultimate design; rather it is to identify a number of designs that may be useful in discussions of cost-effectiveness (Table 4).

One approach is to change the inclusion strategy in clinical trials in order to better reflect the overall population (older and with more comorbidities) so that trial results are more generalizable. At first glance this approach seems feasible, but it is also risky. If the aim is to test disease-modifying effects on AD, it is crucial that the target population in a trial indeed suffers from pure AD. A population that in current clinical practice may be considered to have AD is probably composed of individuals with several conditions that may influence cognition together with an AD process [36], making intervention effects difficult to detect. However, the results will be more generalizable to the whole population.

The results from epidemiological studies highlight the influence of vascular factors in AD. It is well known that the proportion of patients considered to have AD or vascular dementia changes with age (the older the individual, the more the cardiovascular contribution appears to be). However, the findings from epidemiological studies also indicate that vascular issues may be involved in the AD process and that comorbidities are mainly vascular, therefore this discussion of inclusion strategies in trials reflects the controversy of what is AD (which is not the aim of this review). In the Kungsholmen project, when dementia cases were re-evaluated and re-classified in light of the new epidemiological results on risk factors [36], the proportion of pure AD cases without vascular components was only 41% and 'mixed AD' was more common; this finding was substantiated by

the results from population-based clinicopathological studies [37].

Another completely different strategy is to further identify pure AD patients (e.g. with biomarkers) to enrich the target population. If the amyloid and/or tau hypotheses are true and can be confirmed with DMT trials for pure AD, it is likely that the DMT will only be effective in a small population of individuals who are younger than those considered to have mixed AD, Thus the results can be generalized to a small population (but how small remains unclear), making it easier to justify cost-effectiveness of DMT.

Another approach is epidemiological and registry studies. Although from an evidence-based medicine perspective these types of studies are in general rated lower than RCTs (for example, the non-controlled design, risk of selection bias and the chicken and egg discussion for epidemiological studies and registries), they have some obvious advantages. The number of individuals included in registries is generally high and may better reflect the general population than participants in RCTs. Registries can be characterized as (i) care registries (for example recording hospitalizations, visits to open care, death certificates and drug use) and (ii) diagnosis/syndrome-specific (or similar) quality of care registries. Not all registries include data that are useful for cost-effectiveness analyses, but patient registries and linked administrative claims and electronic medical records may provide information about costs and certain consequences of care and management (such as institutionalization and survival) [38]. In Sweden the dementia registry, now including data from more than 25 000 individuals with dementia, has been used for estimates of diagnostic costs [23]. In addition to these general disadvantages with registries, there are always problems with missing data that are crucial from a cost-effectiveness viewpoint (for example lack of data from informal care and relevant outcome measures).

In epidemiological studies the follow-up periods are in most cases much longer than in RCTs (even if the intervals between follow-up are longer) and it may in epidemiological studies be possible to identify patient groups that are or are not on some kind of treatment. Epidemiological studies usually include a comprehensive set of variables that are useful for different regression/covariate testing. Thus, despite the potential to be useful in treatment discussions, epidemiological studies include data that are crucial for estimates of progression rates (that can be used in models). If epidemiological studies also include data about resource use, they can be used for estimates of cost and as inputs in cost-effectiveness models. Combining the control data from trials and integrating them with the findings from register and population cohorts will be a powerful approach in future.

Through simulation models it is possible to translate efficacy data observed in a clinical trial sample to long-term outcomes for a broader population in clinical practice. This is established practice for the evaluation of new pharmaceutical products; decision-making bodies in several countries accept or require evidence from models for the pricing and reimbursement of new pharmaceutical products. Simulation models based on clinical trial data have been developed for clinical AD-dementia [39]. Recent systematic reviews have shown that effects on mortality and time to institutionalization are crucial for cost-effectiveness estimates [40, 41].

However, models focusing on the presymptomatic or MCI stages of AD are rare. Modelling the cost-effectiveness of interventions in the predementia stages of AD requires longitudinal data on progression through the disease stages, resource utilization and quality of life, all of which are rarely available at present. In a model of a hypothetical disease-modifying intervention in AD, the intervention was not found to save costs in the basic option with a prolonged effects on survival, but if it was assumed that there were no such differences in survival, the intervention was cost neutral [34].

Translating clinical trial end-points into measures that are meaningful to patients and policymakers/payers

Cognition, activities of daily living (ADL) capacity, behavioural and psychological symptoms in dementia and global/stage instruments are the traditional and most frequently used efficacy outcomes in clinical trials in AD.

Although quality of life (in a wide context) is regarded as a relevant (or perhaps the most relevant) outcome of treatment of AD for patients as well as for carers, it is seldom used; when used, quality of life has not or has rarely been shown to be significantly affected [16, 41, 42]. Assessment of quality of life is complex. Instruments may be diagnosis specific such as the Dementia Quality of

Life instrument (DQoL) [43], Quality of Life-Alzheimer's Disease (QoLAD) [44], DEMQOL [45] and, in late-stage dementia, The quality of life in late-stage dementia (QUALID) [46] or generic tests such as the Short Form (SF) series [47] or WHOQOL [48]. In cost-effectiveness studies, particularly in modelling, quality-adjusted life-year (QALY) instruments are frequently used such as EQ5D/EuroQol [49], Health Utilities Index (HUI) [50], 15D [51], SF-6D [52] and quality of well-being (QWB) scale [53].

QALYs reflect both quantity and quality of life [54, 55] and the advantage is that there are opportunities for comparisons with other diseases. However, the use of QALYs is not without controversy [56]. Chronic incurable progressive disorders are relatively misfavoured when compared with surgical treatment, for example cataract or hip replacement surgery. Health utility figures may also be difficult to interpret – what does a figure such as 0.546 really mean?

If predementia states are included in cost-effectiveness studies of AD in which QALYs are used, more studies to analyse utilities in these states are needed. It is not clear whether the scales we use today are sensitive enough to detect meaningful changes in quality and quantity of life. Only one study included utility figures for different stages in the Clinical Dementia Rating (CDR) scale (including the CDR stage 0.5, which is rather similar to MCI) [57]. The WHO often uses disability-adjusted life-years (DALYs) [58] instead of QALYs, where the focus is on disability and not quality of life.

Family members of individuals with AD have several roles, besides as next of kin; they act as producers of informal care, but the disease also has an impact on their own situation and quality of life. Thus, it has been debated whether in addition to assessment of their efforts in terms of contribution to informal care (as part of the numerator in the ICER), their own quality of life/QALYs should also be incorporated (as part of the denominator). Although not entirely specific for AD and other dementias, the caregiver's situation is nevertheless an important phenomenon, and in predementia states, it is has been shown that the symptoms of MCI are stressful for caregivers [59], perhaps due to their vague nature and the uncertainty they cause.

Other outcomes such as time to institutionalization ('nursing home postponement') or time to progression of AD/dementia have also been used in pharmacoeconomic analyses [60]. There are two problems with the time to institutionalization as an outcome. First, because the cost of long-term care is one of the major cost drivers in dementia care, it would be part of both the numerator and denominator in an estimate of the cost-effectiveness ratio; secondly, it is extremely dependent on the availability of long-term care institutions and national social policies. In LICs, almost no long-term care is available.

Whether the preferences/viewpoint of the general population or the patients and/or their next of kin/caregivers or others should be the basis for selection of outcomes in a wide context or in the construction of quality of life instruments is debated; this discussion will of course have an impact on the selection of outcomes and on how policy and decision-makers act [61]. A patient may regard loss of cognition and loss of autonomy as the worst outcomes, whereas the caregiver may consider the patient's behavioural problems or loss of ADL more important, and the budget holder may be most concerned with the time to institutionalization. Furthermore, a policymaker may regard quality of life as the most relevant outcome whilst the views within a general population may vary greatly depending on individuals' age, life situation and other factors. The complex interaction between self-rated and proxy-rated quality of life is illustrated in the study by Jonsson *et al.* [62] in which patients themselves rated their quality of life higher than their next of kin/caregivers.

Long-term outcomes and mortality

In most reported trials (mainly on cholinesterase inhibitors) in AD, there are either insufficient data or no differences in mortality between treated and nontreated patients [16, 41]. From epidemiological research, it is known that cognitive impairment, AD and dementias shorten life [63] and at least some dementias can be viewed as part of terminal decline [64]. Thus, it is logical to consider that interventions that alter the course of disease also will have an impact on survival. There are several reasons why such an effect has not been shown previously: earlier interventions have only been symptomatic and not disease modifying, the duration of studies was too short to show effects on mortality and selection bias was present in trials (younger and more healthy), as mentioned above. Patients with AD may live with the disease for

several years and perhaps decades if the preclinical stages are taken into consideration. Thus, it is very difficult to draw any conclusions about effects on survival from clinical trials lasting for short periods (1–2 years). In a chronic progressive disorder such as AD, modelling the long-term consequences of intervention is unavoidable as no RCT will capture all events and record all costs and health-related quality of life effects over the lifetime of the patient. This is particularly true for interventions in the early stages of the disease, where evaluations will need to combine short-term clinical trial data with long-term disease progression through a disease-modelling framework.

Conclusions

An integrated approach that combines available evidence from population and clinical settings is needed to help model the uncertainties of each type of study design. This should provide a guide as to the likely costs and benefits of particular approaches to dementia both now and in the future. Specifically, the following are required. Firstly, long-term population-based data on disease progression, costs and quality of life outcomes in clinical practice starting not only in dementia but also in predementia states; secondly, reliable surrogate end-points in clinical trials that are sensitive enough to detect effects even in predementia states; thirdly, robust and validated modelling methods starting from predementia states and taking into account comorbidities and age, and finally, a discussion of the ethical consequences of early diagnosis.

Conflict of interest statement

Ballard: Consulting work for Acacia, Novartis, Lundbeck Pharmaceutical.

Wimo: Advisory board: Lilly, Nutricia

Consultant: Lilly, Pfizer, Janssen-Cilag, Lundbeck, BMS, Merz, Forest, Novartis, Astra-Zeneca, Sanofi, GSK, Nutricia

The other authors declared no conflicts of interest.

References

1 Prince M, Bryce R, Albanese E, Wimo A, Wagner R, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013; **9:** 63–75.e2.

2 Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet* 2011; **377:** 1019–31.

3 Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM. Is dementia incidence declining?: trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology* 2012; **78:** 1456–63.

4 Matthews FE, Arthur A, Barnes LE *et al.* A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet* 2013; **382:** 1405–12.

5 Wimo A, Jonsson L, Bond J, Prince M, Winblad B. The worldwide economic impact of dementia 2010. *Alzheimers Dement* 2013; **9:** 1–11 e3.

6 Wimo A, Prince M. World Alzheimer Report 2010. The global economic impact of dementia. London; 2010 Contract No.: Document Number|.

7 ADI. World Alzheimer Report 2011. The benefits of early diagnosis and intervention. London; 2011 Contract No.: Document Number|.

8 Banerjee S, Wittenberg R. Clinical and cost effectiveness of services for early diagnosis and intervention in dementia. *Int J Geriatr Psychiatry* 2009; **24:** 748–54.

9 Corbett A, Stevens J, Aarsland D *et al.* Systematic review of services providing information and/or advice to people with dementia and/or their caregivers. *Int J Geriatr Psychiatry* 2012; **27:** 628–36.

10 Dubois B, Feldman HH, Jacova C *et al.* Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 2010; **9:** 1118–27.

11 Sperling RA, Aisen PS, Beckett LA *et al.* Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7:** 280–92.

12 Albert MS, DeKosky ST, Dickson D *et al.* The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7:** 270–9.

13 McKhann GM, Knopman DS, Chertkow H *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7:** 263–9.

14 Wimo A, Jonsson L, Bond J, Prince M, Winblad B. The worldwide economic impact of dementia 2010. *Alzheimers Dement* 2013; **9:** 1–11.e3.

15 Drummond MF, Sculper MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*, 3rd edn. Oxford: Oxford University Press; 2004.

16 SBU. *Dementia. A Systematic Review*. Stockholm: Staten beredning för medicinsk utvärdering (SBU) (The Swedish Council on Technology Assessment in Health Care), 2008. Report No.: 172E/1-3 Contract No.: Document Number|.

17 Hort J, O'Brien JT, Gainotti G *et al.* EFNS guidelines for the diagnosis and management of Alzheimer's disease. *Eur J Neurol* 2010; **17:** 1236–48.

18 Boccardi M, Ganzola R, Bocchetta M *et al.* Survey of protocols for the manual segmentation of the hippocampus: preparatory steps towards a joint EADC-ADNI harmonized protocol. *J Alzheimers Dis* 2011; **26(Suppl 3):** 61–75.

19 Buerger K, Frisoni G, Uspenskaya O *et al.* Validation of Alzheimer's disease CSF and plasma biological markers: the multicentre reliability study of the pilot European Alzheimer's Disease Neuroimaging Initiative (E-ADNI). *Exp Gerontol* 2009; **44:** 579–85.

20 Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, Ince P. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. *PLoS Med* 2009; **6:** e1000180.

21 Brayne C, Davis D. Making Alzheimer's and dementia research fit for populations. *Lancet* 2012; **380:** 1441–3.

22 Andermann A, Blancquaert I, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ* 2008; **86:** 317–9.

23 Wimo A, Religa D, Spångberg K, Edlund A-K, Winblad B, Eriksdotter M. Costs of diagnosing dementia - Results from SveDem, the Swedish Dementia Registry. *Int J Geriatr Psychiatry* 2013; **28:** 1039–44.

24 Wimo A, Winblad B, Engedal K *et al.* An economic evaluation of donepezil in mild to moderate Alzheimer's disease: results of a 1-year, double-blind, randomized trial. *Dement Geriatr Cogn Disord* 2003; **15:** 44–54.

25 Wimo A, Winblad B, Stoffler A, Wirth Y, Mobius HJ. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics* 2003; **21:** 327–40.

26 Feldman H, Gauthier S, Hecker J *et al.* Economic evaluation of donepezil in moderate to severe Alzheimer disease. *Neurology* 2004; **63:** 644–50.

27 Courtney C, Farrell D, Gray R *et al.* Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004; **363:** 2105–15.

28 Cohen JT, Neumann PJ. Decision analytic models for Alzheimer's disease: state of the art and future directions. *Alzheimers Dement* 2008; **4:** 212–22.

29 Olafsdottir M, Skoog I, Marcusson J. Detection of dementia in primary care: the Linköping study. *Dement Geriatr Cogn Disord* 2000; **11:** 223–9.

30 Jagger C, Matthews R, Lindesay J, Robinson T, Croft P, Brayne C. The effect of dementia trends and treatments on longevity and disability: a simulation model based on the MRC cognitive Function and Ageing Study (MRC CFAS). *Age Ageing* 2009; **38:** 319–25; discussion 251.

31 Zhang YL. *Potential Cost-effectiveness of a Health Intervention Program with Risk Reductions for Being Demented*. Stockholm: Karolinska Intstitutet, 2010.

32 Ahtiluoto S, Ngandu T, Rauramaa R *et al.* Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (abstract). 10th International Conference of Alzheimer's Disease (ICAD); 2010; Honolulu, USA, 2010.

33 Nilsson P, Iwata N, Muramatsu S, Tjernberg LO, Winblad B, Saido TC. Gene therapy in Alzheimer's disease - potential for disease modification. *J Cell Mol Med* 2000; **14:** 741–57.

34 Skoldunger A, Johnell K, Winblad B, Wimo A. Mortality and treatment costs have a great impact on the cost-effectiveness of disease modifying treatment in Alzheimer's disease—a simulation study. *Curr Alzheimer Res* 2013; **10:** 207–16.

35 Schneider LS, Olin JT, Lyness SA, Chui HC. Eligibility of Alzheimer's disease clinic patients for clinical trials. *J Am Geriatr Soc* 1997; **45:** 923–8.

36 Aguero-Torres H, Kivipelto M, von Strauss E. Rethinking the dementia diagnoses in a population-based study: what is Alzheimer's disease and what is vascular dementia? A study from the kungsholmen project. *Dement Geriatr Cogn Disord* 2006; **22:** 244–9.

37 Ahtiluoto S, Polvikoski T, Peltonen M *et al.* Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. *Neurology* 2010; **75:** 1195–202.

38 Lin PJ, Neumann PJ. The economics of mild cognitive impairment. *Alzheimers Dement* 2012; **9:** 58–62.

39 Green C, Shearer J, Ritchie CW, Zajicek JP. Model-based economic evaluation in Alzheimer's disease: a review of the methods available to model Alzheimer's disease progression. *Value Health* 2011; **14:** 621–30.

40 Pouryamout L, Dams J, Wasem J, Dodel R, Neumann A. Economic evaluation of treatment options in patients with Alzheimer's disease: a systematic review of cost-effectiveness analyses. *Drugs* 2012; **72:** 789–802.

41 Bond M, Rogers G, Peters J *et al.* The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. *Health Technol Assess* 2012; **16:** 1–470.

42 Shearer J, Green C, Ritchie CW, Zajicek JP. Health state values for use in the economic evaluation of treatments for Alzheimer's disease. *Drugs Aging* 2011; **29:** 31–43.

43 Brod M, Stewart AL, Sands L, Walton P. Conceptualization and measurement of quality of life in dementia: the dementia quality of life instrument (DQoL). *Gerontologist* 1999; **39:** 25–35.

44 Logsdon RG, Gibbons LE, McCurry SM, Teri L. Assessing quality of life in older adults with cognitive impairment. *Psychosom Med* 2002; **64:** 510–9.

45 Smith SC, Lamping DL, Banerjee S *et al.* Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess* 2005; **9:** 1–93, iii-iv.

46 Weiner MF, Martin-Cook K, Svetlik DA, Saine K, Foster B, Fontaine CS. The quality of life in late-stage dementia (QUALID) scale. *J Am Med Dir Assoc* 2000; **1:** 114–6.

47 Spilker B. *Quality of Life and Pharmacoeconomics in Clinical Trials*. Philadelphia: Lippincott-Raven Publishers, 1996.

48 O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. *Qual Life Res* 2000; **9:** 121–4.

49 Coucill W, Bryan S, Bentham P, Buckley A, Laight A. EQ-5D in patients with dementia: an investigation of inter-rater agreement. *Med Care* 2001; **39:** 760–71.

50 Neumann PJ, Sandberg EA, Araki SS, Kuntz KM, Feeny D, Weinstein MC. A comparison of HUI2 and HUI3 utility scores in Alzheimer's disease. *Med Decis Making* 2000; **20:** 413–22.

51 Sintonen H. The 15D instrument of health-related quality of life: properties and applications. *Ann Med* 2001; **33:** 328–36.

52 Walters SJ, Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. *Health Qual Life Outcomes* 2003; **1:** 4.

53 Kerner DN, Patterson TL, Grant I, Kaplan RM. Validity of the Quality of Well-Being Scale for patients with Alzheimer's disease. *J Aging Health* 1998; **10:** 44–61.
54 Torrance G. Designing and conducting cost-utility analysis. In: Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials*. Philadelphia: Lippincott-Raven Publishers, 1996; 1105–21.
55 Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. *Med Care* 1996; **34:** 702–22.
56 Tsuchiya A, Dolan P, Shaw R. Measuring people's preferences regarding ageism in health: some methodological issues and some fresh evidence. *Soc Sci Med* 2003; **57:** 687–96.
57 Ekman M, Berg J, Wimo A, Jonsson L, McBurney C. Health utilities in mild cognitive impairment and dementia: a population study in Sweden. *Int J Geriatr Psychiatry* 2007; **22:** 649–55.
58 Anand S, Hanson K. Disability-adjusted life years: a critical review. *J Health Econ* 1997; **16:** 685–702.
59 Seeher K, Low LF, Reppermund S, Brodaty H. Predictors and outcomes for caregivers of people with mild cognitive impairment: a systematic literature review. *Alzheimers Dement* 2013; **9:** 346–55.
60 Sano M, Ernesto C, Thomas RG *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med* 1997; **336:** 1216–22.
61 Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on cost-effectiveness in health and medicine. *JAMA* 1996; **276:** 1339–41.
62 Jonsson L, Andreasen N, Kilander L *et al.* Patient- and proxy-reported utility in Alzheimer disease using the EuroQoL. *Alzheimer Dis Assoc Disord* 2006; **20:** 49–55.
63 Rizzuto D, Bellocco R, Kivipelto M, Clerici F, Wimo A, Fratiglioni L. Dementia after age 75: survival in different severity stages and years of life lost. *Curr Alzheimer Res* 2012; **9:** 795–800.
64 Brayne C, Gao L, Dewey M, Matthews FE. Dementia before death in ageing societies–the promise of prevention and the reality. *PLoS Med* 2006; **3:** e397.
65 Wilson JMG, Jungner G. *Principles and Practice of Screening for Disease*. [pdf] Geneva: WHO, 1968 [updated 1968; cited]; Available from: http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf.

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